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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1638	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/805,804	BAULCOMBE ET AL.	
	Examiner	Art Unit	
	Ashwin Mehta	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 May 2007 and 27 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *116-124* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *116-124* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/491,549.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submissions filed on February 27, 2007 and May 3, 2007 have been entered. The elected invention of Group I and the elected species of plants continue to be examined in this Office action.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The rejections of claims 33-36, 40, 41, 60-80, 83, and 93-115 under 35 U.S.C. 112, 2nd paragraph are moot, in light of the claim cancellations.

4. The rejection of claims 33, 35, 40, 111, and 112 under 35 U.S.C. 102(b) is moot in light of the claim cancellations.

Specification

5. The amendment to the abstract filed March 17, 2006 remains objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material that is not supported by the original disclosure is as follows: "corresponding complementary short sense RNA molecules" and "include" in the sentence, "The SRMs include short antisense RNA molecules, SARMs and corresponding complementary short sense RNA molecules, SSRMs which are present in at equal abundance, and which are specific for the targeted region of the target gene. There is no written descriptive support for "corresponding complementary" in the originally filed application. The term "include" is open language that suggests something other than SARMs and SSRMs can be a SRM. The specification at page 2, lines 22-26, states that short sense and antisense RNA molecules are collectively SRMs. The specification as originally filed does not describe SRMs as "including" SARMs and SSRMs.

Claim Objections

6. Claim 119 is objected to because of the following informalities: a typographical error appears in line 3 in the term "selected.". Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. Claims 116-124 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 116 and 120: there is insufficient antecedent basis for the recitation, "the cell" in line 1.

In claim 117: there is insufficient antecedent basis for the recitation, "said organism" in line 2.

8. Claims 116-124 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons of record stated in the previous Office actions for (now cancelled) claims 33-36, 40, 41, 60-80, 83, 93-107, and 109-115.

In the paper filed February 27, 2007 Applicants indicate that it is believed that the claims are free of wording that has raised new matter objections in previous claims (page 4, 4th paragraph). In the paper filed May 3, 2007 Applicants indicate that the claims no longer refer to direct complementarity between the SSRMs and the SARMs; that the claims do not require that the SARMs and SSRMs be double-stranded, but also emphasize that double-stranded forms are included within the scope of the claim (page 4, 1st and 2nd paragraphs).

However, the claims still include new matter. Independent claim 116 is drawn to a method of silencing any gene in a cell (plants are the elected species) by post-transcriptional gene silencing (PTGS), wherein the method comprises introducing into said cell short RNA molecules (SRMs) which comprise equimolar amounts of isolated short sense RNA molecules (SSRMs) and isolated short antisense RNA molecules (SARMs); wherein the SARMs are

complementary to a region of a target RNA transcribed from a gene which is silenced when said SRMs are present in a cell containing said gene and said SSRMs correspond to said target RNA; and wherein the SSRMs and SARMs consist of 20-30 nucleotides, whereby said gene is silenced. The term "isolated" in the recitations "isolated sense RNA molecules" and "isolated short antisense RNA molecules" indicates that SRMs are introduced into a plant cell by introduction of the short RNA molecules themselves into the cell, and not by introduction and transcription of a DNA construct encoding said SRMs. Claim 120 is also drawn to a method of silencing a gene in the cell of a plant (the elected species) by PTGS, comprising introducing into said cell a composition comprising isolated short antisense RNA molecules and isolated short sense RNA molecules corresponding to a target RNA transcribed by said gene, the sequence of which consists of 20-30 nucleotides and wherein said SARMs can base pair with said target RNA.

Claim 116 recites, "which SRMs comprise equimolar amounts of isolated short sense RNA molecules (SSRMs) and isolated short antisense molecules (SARMs)". The term "comprise" is an open-ended transitional phrase, and leaves open the possibility that the SRMs encompassed by the claim can be something other than a SARM or SSRM. However, the specification does not describe a SRM as "comprising" SSRMs and SARMs, but rather describes SRMs as being SARMs or SSRMs. Page 2, lines 22-23 states, "...such short sense and antisense RNA molecules (hereinafter, collectively SRMs)". Page 4, lines 20-25 states, "In performing the invention, it may be preferred to analyse or otherwise utilise short anti-sense RNA molecules (SARMs) rather than short sense RNA molecules (SSRMs). Nonetheless, where reference is made herein to SARMs (except where context clearly suggests otherwise) it will be appreciated by those skilled in the art that the SSRMs may also be used." The specification describes SRMs

as SARMs or SSRMs, but does not describe what other type of molecule a SRM can "comprise". The term "comprise" in claim 116 is NEW MATTER and must be deleted.

As mentioned above, Applicants have indicated that double-stranded forms of SARMs and SSRMs are considered to be within the scope of the claims. Previous Office actions have stated reasons why written descriptive support is not found in the application as originally filed for SRMs encompassing double-stranded molecules. Insofar as the term "comprise" in claim 116 encompasses such an interpretation, the issue regarding lack of written descriptive support for SRMs as encompassing double-stranded molecules is maintained. Claims 120-124 are also included in this rejection, insofar as the composition introduced into the cell can comprise double-stranded forms of the isolated SARMs and SSRMs, as argued by Applicants.

Applicants also argue that the specification states that double-stranded RNA is known to induce silencing in nematodes and it concludes that there is a relationship between the SRMs of the invention and silencing in nematodes using double-stranded RNA (response filed May 3, 2007, page 4, 3rd full paragraph). However, the passage on page 3 pointed out by Applicants does not state that SRMs are to be interpreted in the instant specification as being double stranded molecules. The first sentence of Example 1 on page 22 even states, "Analyses were performed to detect low molecular weight antisense RNA in four classes of PTGS in plants using the following general methods" (emphasis added). The example describes how a low molecular weight RNA species estimated to be 25 nt and in antisense polarity to the target ACO mRNA was isolated from plant cells, and that 25 nt RNA of sense polarity at the same abundance as the antisense RNA was also present. However there is no indication, in the specification, that this sense sequence is the complement of the antisense sequence. Page 12, lines 17-20 states "Since

dsRNA induced PTGS is conserved between nematodes, protozoa and insects it is likely that these other organisms which support PTGS may be susceptible to SARMs." Again, a distinction is made here between dsRNA and SARMs. It is further noted that the references cited in the specification in support of the induction of PTGS with dsRNA, teach induction with double-stranded RNA that are clearly much larger than 20-30 base pairs in length.

Applicants also point to the example on page 24 of the specification in which it was concluded that 25 nt antisense GUS RNA is dependent on transcription from the 35S promoter, and argue that the 25 nucleotide SARM must be polymerized using the transcribed sense GUS RNA as a template, and that such polymerization requires double-stranded RNA be formed. Applicants argue that one skilled in the art would view this teaching as confirmation that double-stranded RNA that includes the SARM was present during the PTGS process (response filed May 3, 2007, paragraph bridging pages 4-5). The example in the specification pointed out by Applicants indicates that the 25 nt antisense RNA appears in plants when the target mRNA is transcribed and post-transcriptionally silenced. However, it does not indicate that the specification at the time of filing contemplated introducing SRMs in double-stranded form into a cell to cause PTGS of a target gene. While discussing the RNA template model of PTGS, the specification also stresses that it could not be distinguished whether the antisense RNA is made directly as 25 nt species or as longer molecules that are subsequently processed, and that the precise role of the 25 nt RNA in PTGS remained to be determined conclusively (page 27, lines 18-29).

Written descriptive support is also lacking for the recitation "equimolar amounts" in claim 116. The specification at page 23 states, "25 nt ACO RNA of sense polarity and at the

same abundance as the 25nt ACO antisense RNA was also present only in the PTGS lines." Applicants cite this section of the specification as support for "equimolar amounts" (response filed February 27, 2007, page 4, 2nd full paragraph). However, support is lacking for "equimolar amounts" in the specification. The recitation also represents NEW MATTER and must be deleted from claim 116.

9. Claims 116-124 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, for the reasons of record stated in the previous Office actions for claims 33-36, 76, and 111. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 116 is drawn to a method of silencing any gene in a cell (plants are the elected species) by post-transcriptional gene silencing (PTGS), wherein the method comprises introducing into said cell short RNA molecules (SRMs) which comprise equimolar amounts of isolated short sense RNA molecules (SSRMs) and isolated short antisense RNA molecules (SARMs); wherein the SARMs are complementary to a region of a target RNA transcribed from a gene which is silenced when said SRMs are present in a cell containing said gene and said SSRMs correspond to said target RNA; and wherein the SSRMs and SARMs consist of 20-30 nucleotides, whereby said gene is silenced. Claims 117-119 limit claim 116 by requiring the cells to be contained in a plant (the elected species) and administering the SRMs to the plant; or require the SRMs to be synthetic; or require the target mRNA to be transcribed from an endogenous gene of the plant. Independent claim 120 is drawn to a method of silencing a gene

in a cell of a plant by PTGS, comprising introducing into said cell a composition comprising isolated SARMs and isolated SSRMs corresponding to a target RNA transcribed from said gene, the nucleotide sequences of which consist of 20-30 nucleotides and wherein said SARMs can base pair with said target RNA. Claims 121 limits claim 120 by requiring the SARMs and SSRMs to be present in equal abundance. Claim 122 depends from claim 120, and requires the cells to be contained in the plant, and requires administering the SSRMs and SARMs to the plant. It is noted that this limitation is already recited in claim 120. Claims 123 and 124 limit claim 120 by requiring the SSRMs and SARMs to be synthetic, or by requiring the SARMs to base pair to a target mRNA transcribed from an endogenous gene in the plant.

The specification indicates that the present inventors investigated PTGS of target genes in a variety of silencing mechanisms in different organisms, and that in every case a previously uncharacterized species of antisense RNA, estimated at around 25 nucleotides and complementary to the targeted mRNA, was detected. Corresponding sense RNA molecules were also detected (page 2, lines 12-20). The specification refers to such short sense and antisense RNA molecules collectively as SRMs (page 2, lines 22-23). The specification indicates that SRMs may be synthesized from an RNA template and represent a specificity determinant and molecular marker of PTGS; that because of their correlation with PTGS and the nature of the molecules (short complementary molecules which could base pair with the target RNAs) they are believed to represent a signal and/or inducer or activator of PTGS. SRMs are defined on page 4 as short RNA molecules approximately 25 nucleotides in length, plus or minus 1-5 nucleotides (page 4, lines 4-14). The specification indicates that the invention encompasses a method of silencing a target gene in an organism by introducing SARMs appropriate for the target gene into

the organism in order to induce silencing (page 10, lines 7-9). The specification also indicates that, in performing the invention, it may be preferred to utilize SARMs rather than SSRMs, although it is to be understood that SSRMs may also be used where reference is made to SARMs (page 4, lines 20-25). This indicates that SRMs are single-stranded RNA molecules that are in sense or anti-sense orientation relative to their target sequence. Working Example 1 teaches that transgenic tomato plants were produced that comprised an ACO cDNA sequence operably linked to the CaMV 35S promoter, the transcription of which resulted in co-suppression of the cDNA and endogenous ACO gene. Low molecular weight nucleic acids and a 30-mer ACO antisense RNA oligonucleotide were fractionated, blotted and hybridized with either ACO sense RNA or antisense RNA transcribed from full length ACO cDNA. An ACO antisense RNA of 25 nt was present in extracts from ACO-silenced transgenic lines but absent from non-silenced lines. 25 nt ACO RNA of sense polarity and at the same abundance as the 25 nt ACO antisense RNA was also present only in the PTGS lines. Transgenic tobacco lines carrying GUS transgenes, but exhibiting PTGS of GUS, were also analyzed. Hybridization with a GUS-specific probe revealed that a discrete species of 25 nt GUS antisense RNA was present in the GUS-silenced line, but not in a non-silenced line (pages 22-24).

However, the specification does not enable the silencing of a target gene or inhibition of translation of a gene product by PTGS in a cell, by introducing into the cell single-stranded RNAs that are 20-30 nucleotides long. There are numerous examples in the prior art of inhibiting a target gene by expressing a complete coding sequence, or a fragment thereof, of that gene in anti-sense orientation, or of co-suppressing a target gene by introducing the coding sequence, or a fragment thereof, of the gene in sense orientation. However, there appears to be a

minimum size limit to single-stranded nucleic acids that can trigger PTGS of its target sequence. Klahre et al. (PNAS, 2002, Vol. 99, pages 11981-11986) have shown that 21-nt sense and 22-nt antisense single-stranded nucleic acid molecules could not induce PTGS of their target sequence. Of nucleic acid molecules that small, only double-stranded molecules (siRNAs), which also contain 2- and 3-nt 3' overhangs, could cause silencing (pages 11982-11983). Further, the silencing was highly sequence specific. siRNAs that had mismatches with the target sequence could not trigger silencing (page 11984). While the instant specification teaches that 25 nucleotide SARMs and SSRMs are produced during PTGS in plants, it does not show that such single-stranded nucleic acid molecules can initiate PTGS of the target gene by introducing them in a plant cell. In the absense of further guidance, undue experimentation would be required by one skilled in the art to cause PTGS of a target gene using single-stranded SRMs.

In the response filed May 3, 2007 Applicants address this issue and the citation of Klahre et al. by arguing that no experiment was done demonstrating that a combination of SSRMs and SARMs was or was not able to silence the relevant gene, and therefore the paper does not describe an experiment that conforms to the requirements of the present claims. Applicants also argue that the document demonstrates that in plants gene silencing can be effected by short double-stranded RNAs (page 5, 2nd full paragraph). However, Applicants do not provide any explanation as to why the results of Klahre et al. would be different if it disclosed expressing a combination of SSRMs and SARMs in a plant.

10. Claims 116-124 are rejected under 35 U.S.C. 102(e) as being anticipated by Fire et al. (U.S. Patent No. 6,506,559), for the reasons of record stated in the Office action mailed 26 May 2006 for claims 33-36, 40, 41, 60-62, 64-75, 77-80, 83, 93-101, and 111-114.

Claim 116 is drawn to a method of silencing any gene in a cell (plants are the elected species) by post-transcriptional gene silencing (PTGS), wherein the method comprises introducing into said cell short RNA molecules (SRMs) which comprise equimolar amounts of isolated short sense RNA molecules (SSRMs) and isolated short antisense RNA molecules (SARMs); wherein the SARMs are complementary to a region of a target RNA transcribed from a gene which is silenced when said SRMs are present in a cell containing said gene and said SSRMs correspond to said target RNA; and wherein the SSRMs and SARMs consist of 20-30 nucleotides, whereby said gene is silenced. Claims 117-119 limit claim 116 by requiring the cells to be contained in a plant (the elected species) and administering the SRMs to the plant; or require the SRMs to be synthetic; or require the target mRNA to be transcribed from an endogenous gene of the plant. Independent claim 120 is drawn to a method of silencing a gene in a cell of a plant by PTGS, comprising introducing into said cell a composition comprising isolated SARMs and isolated SSRMs corresponding to a target RNA transcribed from said gene, the nucleotide sequences of which consist of 20-30 nucleotides and wherein said SARMs can base pair with said target RNA. Claims 121 limits claim 120 by requiring the SARMs and SSRMs to be present in equal abundance. Claim 122 depends from claim 120, and requires the cells to be contained in the plant, and requires administering the SSRMs and SARMs to the plant. It is noted that this limitation is already recited in claim 120. Claims 123 and 124 limit

claim 120 by requiring the SSRMs and SARMs to be synthetic, or by requiring the SARMs to base pair to a target mRNA transcribed from an endogenous gene in the plant.

Fire et al. teach a method of silencing a target gene post-transcriptionally in plant cells or plants, comprising introduction of a dsRNA wherein one of the strands is complementary to a portion of the target gene. The method comprises introducing into cells short RNA molecules that are complementary and are in sense and antisense orientation with respect to a portion of the target gene sequence. The RNA molecules are at least 25 nucleotides in length. As the sense and antisense RNA molecules form a double strand, they are present in equal abundance. The target gene may be any gene, including endogenous genes. The RNA may be synthesized chemically, indicating that synthetic short RNA molecules are taught by the reference (col. 6, line 32-col. 8, line 6; col. 8, line 32-col. 9, line 25; col. 11, lines 8-55; claims).

11. Claims 116-124 are rejected.

Contact Information

Any inquiry concerning this or earlier communications from the Examiner should be directed to Ashwin Mehta, whose telephone number is 571-272-0803. The Examiner can normally be reached from 8:00 A.M to 5:30 P.M. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Anne Marie Grunberg, can be reached at 571-272-0975. The fax phone numbers for the organization where this application or proceeding is assigned are 571-273-8300. Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR

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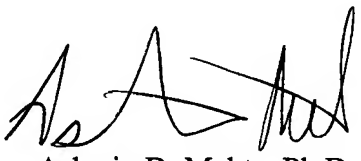

June 21, 2007

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Art Unit 1638